The Recognition and Management of Maternal Sepsis

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Introduction

In 1990, the United Nations set out to reduce maternal mortality by 75 % by the year 2015 [67]. Whilst there has been a notable reduction from approximately 523,000 deaths worldwide in 1990 to 289,000 in 2013, further improvements will have to occur to reach the desired target. 99 % of these deaths occur in developing nations, and a subsection is invariably preventable [71].

Worldwide, between the years 2003 and 2009, an estimated 261,000 (10.7 %) of deaths occurred as the result of maternal sepsis. In developing nations, 10.7 % of maternal deaths were due to sepsis compared to 4.7 % in developed countries [57]. Worldwide the incidence of maternal sepsis is increasing as a 2006 analysis identified the percentage of maternal deaths occurring as the result of sepsis as 2.1 % in developed countries and between 7.7 % and 11.6 % in developing nations [37].

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The incidence of maternal sepsis not resulting in death is harder to estimate but is thought to occur in between 0.1 and 0.6 per 1000 deliveries in developed nations [5]. Whilst still relatively uncommon in comparison to other obstetric emergencies, the mortality rate is significant and can approach to 10 % [66]. In developing nations, the incidence varies between 0.03 % and 0.7 % with a mortality rate of 33.3 % [36].

A recent UK study examining severe maternal sepsis morbidity showed that for every 1 woman who died, 14 suffer life-threatening septic shock. The incidence of severe sepsis was 47 cases per 100,000 and septic shock 9.1 per 100,000 maternities. Patients with Group A Streptococcal infections were more likely to progress to septic shock [3].

Within the UK, whilst the overall maternal mortality rate has fallen from 13.95 per 100,000 maternities in the years 2003–2005 to 11.39 per 100,000 maternities in the 2006–2008 trienniums, the incidence of sepsis-induced deaths increased from 0.85 to 1.13 per 100,000 pregnancies in the same time periods and, in that report, was the leading cause of direct maternal deaths. Substandard care was identified in 69 % of deaths from sepsis in the 2006–2008 trienniums, comparing to 61 % across all cause fatalities [13].

The recently published report into UK maternal deaths from the years 2009 to 2012 has shown a statistically significant reduction in overall maternal deaths to 10.1 per 100,000 pregnancies.

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Almost 25 % of women who died had severe sepsis, and although the most recent rates of fatal genital tract sepsis fell to 0.5 per 100,000 maternities, genital tract sepsis represented less than a quarter of sepsis deaths, with the remainder being caused by influenza and other infections [38].

The significant reduction in the rate of genital tract sepsis is thought to be as the result of increased public and professional awareness of the recognition and management of sepsis through various publications and initiatives [17, 54, 63]. It should be noted with caution, however, that scarlet fever and the resulting increased risk of Group A maternal Streptococcal infection tend to be cyclical in nature, with peaks occurring approximately every 4 years [38]. Ongoing vigilance is therefore imperative.

Sepsis can present at any stage of pregnancy and, given its frequently insidious course, should never be underestimated. Pregnant or recently pregnant women can rapidly descend into fulminant sepsis with resultant multi-organ failure unless early identification and prompt treatment are instituted. Frequently the combination of a young population alongside the physiological changes of pregnancy masks the development and progression of simple infections into life-threatening situations. This chapter will focus on the key messages concerned with the diagnosis and management of maternal sepsis.

Definitions

The Surviving Sepsis Campaign defines sepsis as "the presence (probable or documented) of infection, together with systemic manifestations of infection" and provides a useful diagnostic classification as detailed in Table 21.1 [17]. Severe sepsis is defined as "sepsis-induced tissue hypoperfusion or organ dysfunction", and the features are described in Table 21.2 [17].

Whilst the criteria outlined in Table 21.1 are highly sensitive for sepsis, they have low specificity, and it is vital that they are applied in the setting intended, i.e. suspected or confirmed infection. Little work has been done to validate these criteria in the setting of maternal sepsis, but small studies have shown a sensitivity of 100 % but a specificity of 17 % with a positive predictive value of only 1.7 % in accurately identifying sepsis in pregnancy [42]. Further difficulty in applying these criteria will occur at particular stages of pregnancy, e.g. active labour with additional confounding factors in operation.

In the absence of fully validated criteria for maternal sepsis, it is reasonable to have a high index of suspicion for the presence of sepsis should a mother display these features and, conversely, relevant variables should be actively and regularly sought in women with confirmed or suspected infection in order to determine the current severity and risk of further deterioration from the infection.

Table 21.1 Diagnostic criteria for sepsis [17]

Infection, documented or suspected, and some of the following:
General variables:
Fever (>38.3 °C)
Hypothermia (core temperature <36 °C)
Heart rate >90/min
Tachypnea (>20 breaths/min)
Altered mental status
Significant oedema or positive fluid balance (>20 mL/kg over 24 h)
Hyperglycaemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables
Leucocytosis (WBC count >12,000/μL)
Leukopenia (WBC count <4000/μL)
Normal WBC count with greater than 10 % immature forms
Plasma C-reactive protein more than two sd above the normal value
Plasma procalcitonin more than two sd above the normal value
Haemodynamic variables
Arterial hypotension (SBP <90 mmHg, MAP <70 mmHg or an SBP decrease >40 mmHg)
Organ dysfunction variables
Arterial hypoxaemia (PaO_2/Fio_2 <300)
Acute oliguria (urine output < 0.5 mL/kg/h for at least 2 h despite adequate fluid resuscitation)
Creatinine increase >0.5 mg/dL or 44.2 μmol/L
Coagulation abnormalities (INR >1.5 or APTT >60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count <100,000 μL–1)
Hyperbilirubinaemia (plasma total bilirubin >4 mg/dL or 70 μmol/L)
Tissue perfusion variables
Hyperlactataemia (>1 mmol/L)
Decreased capillary refill or mottling

Table 21.2 Features of severe sepsis (sepsis-induced tissue hypoperfusion or organ dysfunction) [17]

Sepsis-induced hypotension
Lactate >2 mmol/L
Urine output <0.5 mL/kg/h for more than 2 h despite adequate fluid resuscitation
Acute lung injury with PaO_2/FIO_2 <250 in the absence of pneumonia as infection source
Acute lung injury with PaO_2/FIO_2 <200 in the presence of pneumonia as infection source
Creatinine >2.0 mg/dL (176.8 μmol/L)
Bilirubin >2 mg/dL (34.2 μmol/L)
Platelet count <100,000 μL
Coagulopathy (international normalised ratio >1.5)

The 2011 Centre for Maternal and Child Enquiries (CMACE) report into maternal deaths in the UK suggested that any of the following "red flag" signs and symptoms should prompt urgent assessment for underlying sepsis:

- Pyrexia >38 °C or unexplained hypothermia.
- Sustained tachycardia >100/min.
- Breathlessness, particularly a respiratory rate >20/min.
- Abdominal or chest pain.
- Diarrhoea and/or vomiting.
- Reduced or absent foetal movements or absent foetal heart.
- Spontaneous rupture of membranes or significant vaginal discharge.
- Uterine or renal angle pain and tenderness.
- The woman is generally unwell or seems unduly anxious, distressed or panicky.
- Persistent vaginal bleeding and abdominal pain post-delivery.

Whilst these symptoms are not unique to infection, sepsis should be considered in the differential diagnosis and actively ruled out or treated [13]. All pregnant or recently pregnant women who are unwell should have appropriate observations recorded and acted upon [38].

Risk Factors for the Development of Maternal Sepsis

Whilst any pregnant or recently pregnant woman has the potential to develop sepsis, certain women present a higher risk, which should alert the clinician to the need for a high index of suspicion (Tables 21.3 and 21.4).

Table 21.3 Risk factors for maternal death from sepsis (developed countries) [62]

Caesarean section (emergency)
Prolonged rupture of membranes
Retained products of conception
Premature labour or miscarriage
History of pelvic or other infection
Interventions, e.g. cerclage, multiple vaginal examinations
Low income
Obesity
Diabetes
Anaemia
Recent sore throat or upper respiratory tract infection in family
Winter months
Migrants from developing countries

Table 21.4 Risk factors for maternal death from sepsis (developing countries) [62]

Poverty
Young age
First pregnancy
Anaemia
Home delivery without trained birth assistant
Specified traditional birth assistant practices
Failure to recognise severity
Distance from healthcare facilities
Lack of medical resources

As population obesity levels rise, associated maternal complications also increase, including the risk of life-threatening sepsis. In the mid-2000s, the prevalence of maternal obesity in the UK was approximately 20 % [28]. One population-based study identified an odds ratio of 2.12 for obese women developing sepsis in pregnancy after controlling for mode of delivery [1], and another study showed a non-significantly increased odds ratio of 1.6 in overweight woman with a body mass index of 25–30 [40]. This heightened risk has been attributed to the increased risk of wound, genitourinary and uterine infection [1].

In the 2011 CMACE report, 8/29 deaths from sepsis occurred before 24-week gestation. Infection should be considered in all cases of termination of pregnancy or miscarriage where

persistent abdominal pain, pyrexia or ongoing bleeding occurs [13].

Diabetes appears to be a risk factor not only for the development of uncomplicated maternal sepsis but also progression to life-threatening sepsis with a 47 % increase in the risk of developing severe sepsis compared with nondiabetic women [2].

Caesarean section is a well-recognised factor in the development of maternal sepsis through wound, genital tract and intra-abdominal infections but additionally respiratory and urinary tract sources. A population study of 1.6 million mothers identified an adjusted odds ratio of 1.99 for the development of sepsis following Caesarean section compared with vaginal delivery [2].

Risk appears to be cumulative with a 25 % increase in the risk of uncomplicated sepsis and a 57 % rise in the progression to severe sepsis for each additional risk factor encountered [2].

Management Priorities

The priorities in management are outlined in Table 21.5 and will be discussed in further detail below. Appendix 1 describes an algorithm for management of maternal sepsis.

Early Recognition

Early recognition of the mother who is either displaying signs of sepsis or indeed who is at risk of progressive deterioration is vital and requires careful attention to routine observations as well as a high index of suspicion, particularly in high-risk mothers, as discussed previously.

All healthcare workers dealing with pregnant women should have training in the features of and risk factors for maternal sepsis [54].

Table 21.5 Management priorities in maternal sepsis

Early recognition
Aggressive resuscitation and treatment, including early antibiotics
Source control
Early review by senior doctors and midwives

Regular recording of vital signs should occur and include parameters such as temperature, pulse rate, blood pressure and respiratory rate. These should be recorded at all hospital or general practitioner attendances and repeated at an appropriate frequency in those with or at high risk of developing sepsis. Charts should be filed in patient notes and referred to during subsequent attendances [59].

These observations should be recorded on a Modified Early Obstetric Warning Score (MEOWS) chart [54] with an appropriate algorithm for escalation of frequency of observations and alerting relevant clinicians. It is widely known that physiological abnormalities frequently precede critical illness [15] and therefore allow timely intervention by clinical teams from various specialities including midwifery, anaesthetics, obstetrics, critical care and microbiology amongst others.

There are a number of MEOWS charts in use, with one validated and endorsed following the seventh CEMACH report [14]. This relies on a "track and trigger" system, where, if a parameter falls outside a defined threshold, a response is triggered. As a minimum, 12 hourly recording of temperature, blood pressure, respiratory rate, oxygen saturation, conscious level (using the *A*wake, *V*oice, *P*ain, *U*nresponsive scale) and pain scores should be undertaken. A trigger is defined as a single red parameter or 2, less severe, yellow triggers as shown in Table 21.6. The appropriate

Table 21.6 Limits of trigger thresholds for MEOWS parameters [59]

	Red trigger	Yellow trigger
Temperature, °C	<35 or >38	35–36
Systolic BP, mmHg	<90 or >160	150–160 or 90–100
Diastolic BP, mmHg	>100	90–100
Respiratory rate, breaths/min	<10 or >30	21–30
Heart rate, beats/min	<40 or >120	100–120 or 40–50
Oxygen saturations, %	<95	–
Pain score	–	2–3
Neurological response	Unresponsive, pain	Voice

Table 21.7 Response algorithm for MEOWS triggers (1 "Red" or 2 "Yellow" parameters) [59]

Midwife action	Give oxygen 10 L/min
	If pregnant, left lateral tilt
	Record observations every 30 min
	Call obstetric and anaesthetic teams
	Review observation and prescription chart
Medical response	Respond within 10 min
	Confirm observations
	History and examination
	Develop and implement management plan
	Decide on appropriate clinical area to manage patient
	Consider escalation/referral
	Plan for review
	Document in notes

actions to be undertaken are outlined in Table 21.7 and include increased frequency of observations and urgent clinical review. A sample MEOWS chart is provided in Appendix 2 [59].

The overall sensitivity of MEOWS triggers in predicting maternal morbidity was 89 % with a specificity of 79 %. The positive predictive value was slightly lower at 39 %, but the negative predictive value was extremely high at 98 %, suggesting, if used accurately, that most patients with abnormal physiological parameters, as the result of a condition such as sepsis, will be identified [59].

Timely recognition of maternal sepsis has been highlighted through a number of clinical examples as being key in preventing further deterioration and possible death [3].

A thorough clinical history and examination should complement the measured observations with a number of signs and symptoms being particularly important:

- Otitis media or sinusitis precipitating CNS infections
- Rectal or vaginal pain or discharge suggestive of genital tract infections
- Abdominal pain requiring opioid analgesia following vaginal delivery
- Upper tract or respiratory symptoms alerting the clinician to the possibility of *Group A Streptococcus* or influenza [38]

It is vital that even after sepsis has been identified and treated that ongoing recording of observations at appropriate time intervals is continued.

Aggressive Resuscitation and Treatment

The Surviving Sepsis Campaign (SSC) was founded in 2002 in order to increase awareness of sepsis and septic shock and develop guidelines to aid the evidence-based management of the condition with a view to improving morbidity and mortality. The most recent guidelines developed in 2012 [17] provide an update on the assessment and management of patients with sepsis and septic shock.

A major review of 29,000 patients with sepsis showed a significant difference ($p<0.001$) in mortality between sites displaying high compliance with the SSC resuscitation bundle (38.6 %) and low compliance sites (29.0 %) [44].

The Royal College of Gynaecologists endorses the SSC approach to the management of maternal sepsis and has developed a modified resuscitation bundle to be implemented within the first 6 h of the diagnosis of sepsis, "The Sepsis 6" (Table 21.8) [54].

Table 21.8 Resuscitation bundle: tasks to be carried out within the first 6 h of diagnosis

Obtain blood cultures prior to antibiotic administration
Administer broad-spectrum antibiotic within 1 h of recognition of severe sepsis
Measure serum lactate
In the event of hypotension and/or a serum lactate >4 mmol/L, deliver an initial minimum 20 mL/kg of crystalloid or an equivalent to target a mean arterial pressure of >65 mmHg
Apply facial oxygen to maintain oxygen saturation
In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate >4 mmol/L
(a) Achieve a central venous pressure (CVP) of ≥8 mmHg
(b) Achieve a central venous oxygen saturation (SvO2) ≥70 %

Obtain Blood Cultures Prior to Antibiotic Administration

The rationale for obtaining blood cultures prior to antibiotic administration lies in the fact that although between 30 % and 50 % of patients with severe sepsis have a bacteraemia at presentation [17], the yield can be reduced by as much as 50 % if antibiotics precede the culture sample [45]. The caveat to this recommendation is that unnecessarily delaying antibiotic therapy in order to obtain a blood sample for culture is potentially harmful and should not occur. An opportune time to obtain blood for culture is at the time of establishing intravenous access in order to administer antibiotics. The process should be undertaken using aseptic precautions in order to avoid sample contamination.

If the patient has other indwelling lines, particularly central venous lines, additional samples should be drawn from these devices and thought given to their removal or replacement if they represent a likely source of infection. Alternative sources of infection should be considered and relevant samples obtained if possible, for example, urine, sputum and vaginal and wound swabs. As before, antibiotic administration should not be delayed unnecessarily in order to obtain these samples.

In addition to obtaining blood for culture, other relevant samples according to clinical history should be analysed for the presence of infective organisms and include sputum, urine, breast milk, vaginal, throat or wound swabs, cerebrospinal fluid and stool samples. Whilst these are not as time critical as obtaining blood for culture, they should be obtained as early as possible.

Administer Broad-Spectrum Antibiotic within 1 h of Recognition of Severe Sepsis

Whilst obtaining relevant culture samples is vital, initial antibiotic choice will invariably be empirical, based on the likely source, patient characteristics and, most importantly, local guidelines. Culture results will allow rationalisation of antimicrobial cover but frequently are not available for a number of hours or even days and therefore are often not useful in the early management of maternal sepsis.

Studies have demonstrated a mortality benefit when antibiotics are administered early in patients with severe sepsis [43], and in fact some studies have demonstrated a measurable increase in mortality for each hour delay in antibiotic administration that occurs [17].

The most common organisms present in women dying from sepsis are *Lancefield Group A beta-haemolytic Streptococcus*, *Streptococcus pneumoniae* and *E. coli* [13, 38]. Mixed infections are possible, and the likely causative organisms in prolonged rupture of membranes, urinary tract infections and cerclage are C*oliform* spp. Severe skin infections may be caused by S*taphylococcal* spp. with the less common but highly lethal *Clostridium perfringens*, the cause of gas gangrene also prevalent. Other anaerobic genital tract infections include *Bacteroides* spp. [54].

Any pre-existing allergies should be sought and antimicrobials adjusted accordingly, and in addition, caution should be exercised in pregnant or breastfeeding mothers. Local microbiology services should be consulted for advice in challenging circumstances.

Suggested empirical antimicrobials are listed in Table 21.9 [13].

Patients at risk of hospital-acquired or multidrug-resistant pathogens include those who are immunocompromised, residents in long-term healthcare facilities and frequent or prolonged hospital admissions. Advice should be sought from hospital microbiology services with consideration given to local guidelines if these pathogens are suspected.

The antimicrobial regime should be reassessed after 48–72 h using microbiological and clinical data, with an attempt made to rationalise the drugs to target both the severity of the infection and the causative organisms if identified. The total duration of antimicrobials will typically be around 7–10 days [17].

Measure Serum Lactate

Elevated serum lactate is indicative of inadequate tissue oxygenation, and a level of >4 mmol/L,

Table 21.9 Suggested empirical antimicrobials for maternal sepsis [13]

Unknown organism and the woman is not critically ill	*Co-amoxiclav* (1.2 g 8 hourly) plus *Metronidazole* (500 mg 8 hourly)
	or
	Cefuroxime (1.5 g 8 hourly) plus *Metronidazole* (500 mg 8 hourly)
	or
	Cefotaxime (1–2 g 6- to 12 hourly) plus *metronidazole* (500 mg 8 hourly)
In cases of allergy to penicillin and cephalosporins	*Clarithromycin* (500 mg 12 hourly)
	or
	Clindamycin (600 mg to 1.2 g by intravenous infusion three or four times daily)
	plus
	Gentamicin (3–5 mg/kg daily in divided doses every 8 h by slow intravenous injection)
Severe sepsis or septic shock	*Piperacillin–tazobactam* (4.5 g 8 hourly)
	or
	Ciprofloxacin (600 mg 12 hourly)
	plus
	Gentamicin
	or
	Meropenem (500 mg to 1 g 8 hourly by intravenous injection over 5 min) plus *gentamicin*
Suspected Group A Streptococcal infection	*Clindamycin* (600 mg to 1.2 g by intravenous infusion three or four times daily) is more effective than penicillin as it inhibits exotoxin production

even in the absence of hypotension, is correlated with poorer outcomes because of either increased severity of illness or inadequate treatment [60]. Goal-directed treatment targeted to a reduction in serum lactate within the first 6 h of diagnosis has been shown to significantly reduce 60-day mortality from sepsis [31]. Serum lactate levels are not altered significantly from normal ranges in healthy pregnant women [5], although may transiently rise immediately following delivery [38].

In addition to the measurement of serum lactate, blood should be sent for full blood picture, urea and electrolytes, liver function tests, coagulation screen, arterial blood gas, C reactive protein and major cations such as magnesium and calcium. These should be repeated at appropriate intervals if abnormalities are detected or if there is a significant change in clinical parameters.

In the event of hypotension and/or a serum lactate >4 mmol/L, deliver an initial minimum 20 mL/kg of crystalloid or an equivalent to target a mean arterial pressure (MAP) of >65 mmHg.

Fluid resuscitation using boluses of 20 mL/kg should begin as early as possible with some patients requiring repeated fluid boluses using a MAP of 65 mmHg as a target [17]. Whilst persistent hypotension may be as the result of intravascular depletion, other possible causes such as loss of vasomotor tone and myocardial depression as the result of septic mediators should be considered. Other alternative causes include haemorrhage, oxytocic drugs and renal failure [13].

Whilst MAP >65 mmHg is an achievable and appropriate target, other suggested endpoints to fluid resuscitation include lactate levels, skin perfusion, mental status and, importantly, urine output [17].

The optimal MAP target in pregnant women with sepsis has not been widely studied, and given that the maternal population is often younger with fewer co-morbidities than general patients with sepsis, it is possible that lower MAP values may be well tolerated. In the absence of robust clinical data, it is reasonable to continue to target a MAP of 65 mmHg [5].

The choice of resuscitation fluid is the subject of ongoing debate, particularly with respect to colloids versus crystalloids. Recent evidence showed a significant increase in mortality from 43 % to 51 % when starch-based colloids were used for resuscitation in severe sepsis compared with crystalloids. There was also an increased need for the use of renal replacement therapy (22 % vs. 16 %) in patients given starch-based colloids [51]. Other published evidence has led to the SSC recommendation that starch-based colloids should be avoided in sepsis with crystalloid fluids used in preference [7, 27, 48].

Albumin may be considered as a resuscitation fluid, particularly when large volumes of crystalloids have been administered [17]. Albumin was

shown to be as safe and effective as 0.9 % saline when used in septic patients in a randomised controlled trial [23], with a non-significant trend towards reduced mortality (OR 0.82) with albumin compared to other fluids in a large *meta*-analysis. Subgroup analysis comparing albumin to crystalloid resuscitation showed a significant reduction in mortality with albumin (OR 0.78) [16]. A large randomised trial published after the most recent SSC update did not identify a survival benefit when albumin was used in addition to crystalloids [8]. This may influence future SSC recommendations.

Accurate fluid balance is essential with all administered fluids both enteral and parenteral being recorded along with fluid output such as blood and gastrointestinal loss in addition to regular, preferably hourly urine output [13].

Whilst women with severe sepsis or septic shock will frequently require large volume fluid resuscitation, fluid overload may lead to fatal pulmonary or cerebral oedema. Features suggestive of fluid overload can be difficult to separate from the features of sepsis but may include a sustained elevation in respiratory rate or persistently low oxygen saturations despite high-flow oxygen. If fluid overload is suspected and arterial hypotension persists, involvement of the critical care team may be necessary, with the use of vasoactive drugs to maintain blood pressure considered [13].

Vasopressors may be required in the face of life-threatening hypotension even when circulating volume has not yet been adequately restored, but are most commonly used when hypotension persists, despite adequate fluid resuscitation. Noradrenaline administered via a central line as an infusion is recommended to aid perfusion pressure, targeting a MAP of 65 mmHg, and will invariably require the involvement of critical care specialists. Second-line agents include adrenaline and vasopressin, although again, these should only be used in specialist critical care areas. Dopamine is not considered for routine use but may be used as an alternative agent in selected patients such as those with bradycardic side effects from noradrenaline. In patients with impaired cardiac output resulting from myocardial dysfunction, dobutamine may be beneficial to aid with inotropy, although again, this should occur in a specialist area [17].

Apply Facial Oxygen to Maintain Oxygen Saturation

Initially, high-flow oxygen via a facemask should be applied, and this can be down titrated according to arterial blood gas results and oxygen saturations. Consideration should be given to the use of humidified oxygen to aid comfort and sputum clearance, particularly when oxygen therapy is required for a number of hours or days.

In the Event of Persistent Hypotension Despite Fluid Resuscitation (Septic Shock) and/or Lactate >4 mmol/L

(a) *Achieve a central venous pressure (CVP) of ≥8 mmHg*
(b) *Achieve a central venous oxygen saturation ≥70 % (SvO_2)*

If hypotension with MAP <65 mmHg persists despite adequate fluid resuscitation and vasopressor use, additional resuscitation endpoints should be considered. Patients in this category will invariably have had input from critical care specialists and will be monitored in a high dependency area.

Severe sepsis can be associated with either an abnormally high or low SvO_2, either because of inadequate oxygen delivery due to reduced global cardiac output or altered microcirculatory oxygen delivery or as the result of reduced tissue oxygen extraction owing again to impaired tissue perfusion or direct septic mediator effects.

The SSC campaign is based around the data published by Rivers in 2001 identifying measurable benefit with the use of early goal-directed therapy (GDT). When early GDT was implemented, mortality was reduced from 46.5 % to 30.5 % ($p = 0.009$) and targets such as SvO_2 >70 % and CVP >8 mmHg were resuscitation endpoints in this study. Patients in the early GDT group received more fluid therapy (5 vs. 3.5 L, $p < 0.001$), suggesting the relationship between early aggressive fluid resuscitation and survival [53].

Two recent large randomised controlled trials have, however, failed to confirm the benefit seen with early GDT. The ProCESS trial compared the use of early GDT, protocol-based standard care with usual care in patients with septic shock and demonstrated no difference in either 90-day- or 1-year mortality or the need for organ support [74]. The ARISE trial confirmed these findings and again compared early GDT with usual care in patients with septic shock, with no difference found in 90-day mortality [64].

Following these publications, the SSC have made the following recommendations:

- Monitoring and targeting CVP and SvO_2 does not necessarily confer survival benefit in patients with sepsis and is no longer evidence based.
- No harm was identified in using these parameters.
- No changes have been made to the current SSC guidelines, but modifications may occur with future updates [17].

Source Control

Source control is the process of definitively managing the focus of infection, frequently utilising surgical intervention. Potential foci of infection are outlined in Table 21.10 [5].

Table 21.10 Potential foci of infection in maternal sepsis [5]

Source	Response
Chorioamnionitis	Delivery of baby
Retained products of conception	Evacuation
Retained placenta (despite medical management)	Manual evacuation
Uterine or bowel injury (usually postpartum)	Laparotomy
Wound infection	Debridement
Incomplete miscarriage	Medical or surgical evacuation
Severe mastitis/breast abscess	Consider incision and drainage
Perineal abscess	Incision and drainage
Genital tract trauma with infection/abscess	Debridement and/or drainage

Review by Senior Doctors/Midwives

It goes without saying that it is inappropriate for junior staff to manage high-risk women without the support of more experienced colleagues as well as outside referral to additional teams such as critical care, microbiology and general medicine. This was highlighted as a key area of management in the most recent MBRRACE report and consultant-to-consultant referral considered appropriate when specialist advice is needed [38].

Supportive Therapy

There are a number of additional areas of focus that should be attended to when managing a woman with severe sepsis or septic shock, most of which are common to the care of any patient with a critical illness. These are outlined in Table 21.11.

Glucose Control

Within the general population with severe sepsis or septic shock, the recommendation is to maintain blood glucose levels less than 180 mg/dL, having commenced protocolised insulin therapy when two consecutive readings are greater than 180 mg/dL. Blood glucose levels should be monitored every 1–2 h following commencement of insulin therapy until stabilised; following which, 4-hourly monitoring should be undertaken [17]. The choice of insulin therapy should conform to local hospital protocols but consideration given to the use of continuous intravenous insulin infusions alongside intravenous fluids containing potassium. Careful monitoring of electrolytes particularly serum potassium and sodium levels as well as fluid balance should be undertaken.

Table 21.11 Supportive therapy in severe sepsis [17]

Glucose control
Venous thromboembolism prophylaxis
Stress ulcer prophylaxis
Avoiding anaemia

The target of 180 mg/dL is based on evidence from the NICE-SUGAR trial, which identified an increased mortality when blood glucose levels of less than 110 mg/dL ("intensive insulin therapy") were targeted in comparison to the more modest 180 mg/dL. The increased mortality was felt to be secondary to the significantly higher incidence of inadvertent hypoglycaemic episodes seen when lower blood glucose targets were used [65]. Whilst subsequent *meta*-analyses did not confirm this higher level of mortality, no reduction in mortality and therefore patient benefit was seen when intensive insulin therapy was instituted [26, 35].

Whilst the use of capillary samples to obtain blood for glucose analysis is convenient, caution should be exercised in patients with severe sepsis in whom peripheral circulation is compromised, leading to falsely elevated or lowered capillary glucose levels. In these patients, serum glucose levels should be monitored [17].

Pregnant women, particularly obese women, are at risk of the development of impaired glucose tolerance even in the absence of a formal diagnosis of diabetes mellitus, and in physiological states, blood glucose levels may be higher than the non-pregnant population. The recommendations described here are validated in the non-pregnant population, but, in the absence of large-scale evidence, can be extrapolated to the pregnant population with severe sepsis.

Venous Thromboembolism Prophylaxis

Pregnant women with severe sepsis are at a significantly increased risk of venous thromboembolism on account of the combined effects of pregnancy and critical illness. Whilst a full discussion on the use of venous thromboembolism prophylaxis is beyond the scope of this chapter, it is important to briefly discuss its role.

The choice of pharmacological agent will depend on local protocols, but head-to-head studies in the non-pregnant acutely ill population suggested a reduction in the incidence of pulmonary embolism (hazard ratio 0.51) when low molecular weight heparin was used in comparison to unfractionated heparin, although no significant difference in the incidence of deep venous thrombosis was seen [50, 52]. Choice of both agent and dose may need to be adjusted in the presence of kidney injury.

The timing and nature of delivery, including the use of neuraxial blockade, will need to be considered when selecting the drug, dose and frequency.

The use of non-pharmacological methods such as sequential compression devices and graduated compression stockings is recommended in addition to pharmacological agents [50] and is of particular importance when these agents are contraindicated, e.g. major haemorrhage, thrombocytopenia, etc. [17, 34].

Stress Ulcer Prophylaxis

Again, this topic will not be discussed in detail in this chapter, but consideration should be given to the use of pharmacological agents to prevent the development of stress-induced gastric ulceration. Risk factors include coagulopathy, mechanical ventilation and hypotension as well as pre-existing peptic ulceration, and should a woman display these risk factors, consideration should be given to the use of H2-receptor antagonists for prophylaxis [17].

Avoiding Anaemia

It is widely accepted that in the non-bleeding pregnant woman, red cell transfusion should not be considered unless haemoglobin levels are less than 70 g/L [33]. A large multicentre trial comparing transfusion thresholds of 70 and 90 g/L in patients with septic shock found no difference in mortality, ischaemic events and use of life support, suggesting a threshold of 70 g/L is safe in the non-bleeding septic pregnant woman [29].

Adjunctive Therapies

Additional adjunctive therapies are found in Table 21.12.

Table 21.12 Adjunctive therapies in maternal sepsis [17, 54]

Steroid therapy
Intravenous immunoglobulin

Steroid Therapy

The use of steroid therapy in sepsis remains controversial. Initial studies suggested a mortality benefit when steroid therapy was instituted in septic shock unresponsive to vasopressor therapy [4], but this benefit was not confirmed in a large multicentre trial, although this trial included all patients with septic shock rather than just those with vasopressor-resistant shock. Whilst the time to resolution of normotension was faster, there was an increased incidence of superinfection with additional microorganisms with a relative risk of 1.27 [61].

Given that only a small minority of women with maternal septic shock fall into the category of vasopressor-resistant shock, the use of steroid therapy will not be applicable to the vast majority of patients. Consideration of the effects of steroid therapy on maternal blood glucose as well as foetal effects should be made.

Currently the surviving sepsis campaign recommends the use of low-dose steroid therapy in critically unwell patients if septic shock persists despite adequate fluid resuscitation and the use of vasopressor infusions [17].

Intravenous Immunoglobulin

Certain bacteria relevant to maternal sepsis modulate their effects through the production of exotoxins, in particular *Staphylococcus* spp. and *Streptococcus* spp. Immunoglobulin therapy acts through immunomodulation, inhibition of production of tumour necrosis factor and interleukins as well as neutralisation of the superantigen effect of exotoxins [54]. Both the Department of Health [19] and the RCOG [54] recommend the use of intravenous immunoglobulin in severe invasive staphylococcal or streptococcal infection if other therapies have failed. There is no evidence for its use in other, particularly Gram-negative infections, and it is contraindicated in congenital deficiency of immunoglobulin A.

Patient Location and Monitoring

The decision of where to manage the patient will depend on several factors including:

- The severity of the patient's condition including the presence of one or more organ failures
- The stage of pregnancy or labour
- Local arrangements and provision including staffing numbers and skill mix

Whilst not exhaustive, some indications for transfer to the critical care unit are outlined in Table 21.13.

The minimum level of monitoring that should be undertaken is outlined in Table 21.14 but should be adapted according to the needs of the situation.

Infection Control Issues

Infection control measures such as hand washing and equipment sterility are common to the management of all patients with maternal infections. In

Table 21.13 Indications for transfer to critical care in maternal sepsis [54]

System	Indication
Cardiovascular	Persistent hypotension or lactaemia despite adequate fluid resuscitation suggesting the need for vasopressor or inotropic therapy
Respiratory	Pulmonary oedema
	Mechanical ventilation
	Airway protection
Renal	Severe acute kidney injury
	Dialysis
Neurological	Decreased conscious level
Miscellaneous	Multi-organ failure
	Uncorrected acidosis
	Persistent hypothermia

Table 21.14 Minimum monitoring standards in severe maternal sepsis

Observation	Frequency
Regular observations including conscious level, respiratory rate, oxygen saturations, heart rate, blood pressure, temperature	Hourly (or more often if unstable)
Urine output	Hourly
Blood tests including renal function, electrolytes, full blood picture, arterial blood gas, coagulation screen, lactate	Twice daily (more often if abnormal)

any case of suspected or confirmed maternal sepsis, the neonatal team should be informed to ensure optimum management of the baby. Some general infection control measures are found in Table 21.15.

Invasive Group A Streptococcal infection is a notifiable disease in the UK, and advice should be sought from local infection control and microbiology teams. As a minimum, the affected woman should be managed in a single room should facilities exist for her safe management, with scrupulous attention to hand hygiene. Healthcare workers should wear fluid repellent surgical masks with visors at delivery. The neonatal team should be informed to enable prophylaxis for the baby, and close personal and healthcare worker contacts should be monitored for symptom development to enable early treatment if necessary [54].

Specific Causes of Maternal Sepsis

The various aetiologies of maternal sepsis are outlined in Table 21.16 and discussed further below. Some of the specific presenting features will be described, but it is important to recognise the often non-specific presentation of sepsis and to actively seek the features of sepsis described previously. Regardless of the cause, the role of early antimicrobials and other treatments as already discussed is vital.

Of note, delay in surgical intervention in genital tract sepsis was noted as a contributing factor in the deaths of several women in the recent MBRRACE report [38] and, as a result, should be considered early in the management of women with chorioamnionitis, endometritis, retained products of conception and surgical wound infections.

Table 21.15 General infection control measures to reduce maternal sepsis [30]

Purpose	Infection control measure
Avoidance of infection	Identification and reduction of risk factors for maternal sepsis
	Hand hygiene
	Surgical asepsis
	Environmental improvements
	Clean equipment
	Antibiotic prophylaxis
	Training of traditional birth attendants
Early detection of infection	Clinical monitoring
	Screening and treatment for *Group B Streptococci* colonisation
	Screening and treatment for bacterial vaginosis
	Treatment of chorioamnionitis before and during labour
Reduction of complications	Barrier nursing of infected individuals
Behavioural and organisational change	Issue of guidelines
	Training
	Audit/quality improvement

Table 21.16 Specific aetiology of maternal sepsis

Pregnancy related	Chorioamnionitis
	Endometritis
	Retained products of conception including septic abortion
	Wound infection
	Mastitis
Non-pregnancy related	Influenza
	Pneumonia
	Pharyngitis
	Appendicitis
	Cholecystitis
	Pyelonephritis
	Meningitis
Low-income countries	TB
	HIV
	Malaria

Chorioamnionitis

The intrauterine infection, chorioamnionitis, usually results from ascending polymicrobial infection in the setting of ruptured membranes; however, it can occur with intact membranes following invasive procedures or haematogenous spread [46]. The prevalence is thought be around 4 % of all maternities, but complicates up to 10 % of preterm deliveries [21].

Risk factors include prolonged rupture of membranes, *Group B Streptococcus* colonisation, young age, prolonged labour, nulliparity, multiple vaginal examinations, meconium-stained amniotic fluid and bacterial vaginosis. Causative organisms include *Group A and B streptococcus*, anaerobes such as *Bacteroides*, *Mycoplasma* and *E. coli* [46].

Presentation can be non-specific but may include pyrexia, abdominal tenderness, foul smelling liquor and foetal tachycardia or distress. The sequelae of chorioamnionitis involve both maternal and foetal effects, with increased Caesarean section delivery (two to three times more likely), wound infection, pelvic abscess, haemorrhage and maternal or foetal bacteraemia [46].

Women remain at risk following Caesarean delivery as the uterine repair creates an anaerobic environment in which pathogens can thrive. If antibiotic therapy fails, consideration of abscess formation or indeed distant infection should be considered with surgical intervention as appropriate [6].

Endometritis

Endometritis refers to infections of the *endo*-, *myo*- and *peri*-metrium. It frequently presents post-delivery following ascension of bacteria from the genital tract during labour, with colonisation of the decidua and amniotic fluid [46].

The infection is most commonly mixed with both anaerobes (*Peptostreptococcus*, *Bacteroides* and *Clostridium* spp.) and aerobes (*Group B streptococcus*, *Group A streptococcus*, *Enterococcus* and *E. coli*) contributing. Severe infections complicate haematoma formation or the presence of devitalised tissue and can include *Streptococcus pyogenes* and *Staphylococcus aureus*.

Again a high index of suspicion is required for diagnosis, but features may include tachycardia, uterine tenderness and purulent vaginal discharge. It should be noted that uterine tenderness may be absent in severe cases of *Group A Streptococcal* infection, due to denervation of the uterus [6].

Of women developing pyrexia after delivery, only 20 % of patients following a vaginal delivery are diagnosed with endometritis compared to 70 % of those following Caesarean section delivery [46]. Patients with endometritis following Caesarean section are particularly at risk of pelvic abscess formation and peritonitis. Ninety percent of women respond to antibiotic therapy, but if there is no, or an inadequate, response to appropriate anti-microbial therapy after 48–72 h, consideration for further imaging such as a CT scan should be undertaken [46].

Retained Products of Conception including Septic Abortion

The infection of septic abortion is mediated through metritis and can follow incomplete miscarriage or intentional abortion. Patients may present 2–7 days following abortion or miscarriage with non-specific symptoms such as abdominal pain, nausea and fever, and although often present, the patient may not volunteer other symptoms such as vaginal discharge [46].

Both legal and illegal abortions carry huge emotional consequence, and patients may try to conceal the nature of original procedure, requiring careful questioning, management and support.

Source control is of particular importance in this condition with urgent evacuation of retained products of conception being life-saving. Hysterectomy may be required if gas-forming infection is suspected, and this is indicated by a dusky, devitalised uterus with crepitus in the surrounding tissues [46].

Regulation of abortion services is vital in reducing the risks associated with this procedure. In the USA, patients are screened and treated for gonorrhoea and chlamydia when presenting for medical abortion, with a proven reduction in infection rates following the introduction of this policy [24].

Wound Infection

Although the use of prophylactic antibiotics during Caesarean section has reduced the risk of postoperative wound infections, they still occur in up to 6 % of deliveries, most commonly in urgent Caesarean sections in women with ruptured membranes [22]. Other risk factors include increased blood loss, longer operating times, obesity, diabetes mellitus, immunosuppression, smoking, anaemia and low socioeconomic class [46].

Causative organisms are often derived from the endogenous vaginal tract flora and include both Gram- positive and Gram-negative organisms as well as facultative anaerobes [46]. Recurrent abscess formation is a feature of *Panton-Valentine leukocidin-producing Staphylococcal* infection and should be considered in unusual or severe cases [54].

Antibiotic therapy will be sufficient in the majority of cases with consideration given to abscess formation if symptoms persist or worsen after the fourth postoperative day. Imaging or incision and drainage may be required [46].

Necrotising fasciitis is amongst the most feared complication of wound infection and occurs due to rapidly spreading infection of the tissues down to the deep fascia. Typical but not universal signs include extreme pain out of keeping with clinical signs, purple skin discolouration, tissue crepitus and bullae formation. Polymicrobial infections are often involved, but the most common organisms are *Group A Streptococcus* species, *Staphylococcus aureus*, and *Clostridium perfringens* [6]. Urgent, often extensive, surgical debridement can be life-saving, with input from local microbiology services vital. In addition to appropriate antibiotics, immunoglobulin therapy may be indicated.

Although not technically "wounds", intravenous cannula, drains and other invasive devices are a potential source of infection and should be regularly inspected for signs of erythema, pain and discharge. Removal is key in controlling infection, but antibiotics may be needed in addition.

Mastitis

Frequently mastitis is overlooked as a cause of severe sepsis but in the 2011 CMACE report identified two women who died as the result of mastitis-related sepsis, one from *Group A Streptococcus* and the other *S. aureus* [13]. The RCOG recommends that all women with severe mastitis displaying systemic symptoms or those not responding within 48 h to oral antibiotics be referred to hospital for assessment [54].

It often is unilateral and usually presents 1-week postpartum. Clinical features include thickening and hardening of the affected breast, erythema and severe pain and are often preceded by engorgement. *Staphylococcus aureus* is the most common pathogen, but consideration should be given to the involvement of *methicillin-resistant Staphylococcus aureus*, particularly if the woman or neonate had a prolonged hospital admission [46].

Breast milk should be sent for culture and sensitivity along with skin swabs and intravenous antibiotics commenced if the woman has been admitted to hospital. Breast pumping may be beneficial and consideration given to incision and drainage if abscess formation has occurred [46].

Influenza

Between 2009 and 2012, 36 women in the UK died as the result of influenza during the pandemic, and these deaths accounted for 43 % of all deaths from sepsis. Of the women that died, 33 had suspected or confirmed influenza A and 3 had influenza B. Influenza is highly infectious and tends to follow a seasonal pattern, with highest prevalence during winter months [38].

Risk factors identified as causing a more severe clinical picture included pregnancy, obesity, asthma and patients with heart disease. Pregnancy in particular resulted in more severe disease with a four times higher rate of hospital admission and seven times higher rate of intensive care admission in pregnant women with influenza [38].

In 94 % of the women who died in the recent pandemic, influenza was not considered as a cause at initial presentation, leading to delays in diagnosis and treatment [38]. A high index of suspicion should be maintained when women present with respiratory symptoms during times when the community prevalence of influenza is high, with appropriate investigations undertaken. Presenting symptoms can include shortness of breath, fever, myalgia, dry cough and headache, possibly with recent infective contacts.

Influenza vaccination is recommended in pregnancy with evidence to suggest a reduction in maternal morbidity and mortality and improved foetal outcomes including reduced likelihood of premature birth, low birth weight and influenza infection as a neonate [47, 49]. None of the women who died from influenza in the MBRRACE report were vaccinated [38], and as 62 % of deaths occurred after the vaccination programme started, some of these deaths may have been preventable.

The use of neuraminidase inhibitors, such as oseltamivir and zanamivir, in the management of influenza has remained controversial, and pregnant women were excluded from most trials evaluating their use. Observational evidence suggests benefit with the early use of neuraminidase inhibitors [75], and both the Department of Health and RCOG recommend their use in pregnant women with signs of influenza, preferably within 48 h of the onset of symptoms, even in the absence of confirmed infection [18]. Zanamivir is the recommended drug of choice in pregnancy, with oseltamivir suggested for women with asthma, chronic obstructive pulmonary disease or severe complicated H1N1 influenza [18]. These drugs appear safe for both mother and baby when taken in pregnancy based on current evidence [38].

Pneumonia

A number of physiological changes of pregnancy render a woman at greater risk of respiratory infections compared to the non-pregnant women and include increased respiratory demand, reduced chest excursion, reduced functional residual capacity and reduced respiratory reserve. Not only do they increase the risk of infection, they can exacerbate the clinical course of the condition. It is estimated to complicate up to 1.5 per 1000 pregnancies in the USA [32].

All common pathogens involved in the development of pneumonia are causative organisms in pregnancy and include *Streptococcus pneumonia,* which tends to cause pyrexia and a cough productive of rust-coloured sputum, and the atypical pathogens including *Mycoplasma*, which tends to result in a non-productive cough, rash and myalgia [6]. Rarely PVL-associated staphylococcal necrotising pneumonia may occur, carrying a mortality of 70 % in otherwise healthy individuals [54].

A chest x-ray should be considered alongside involvement of respiratory physicians and chest physiotherapists to ensure optimum treatment. Sputum for culture alongside urine for antigen testing, if available, should be sent.

Viral pneumonia can also occur in pregnancy, although albeit uncommonly. *Varicella zoster* pneumonia in pregnancy requiring mechanical ventilation can have a mortality of up to 14 % despite optimal treatment [41]. Chest x-ray may show widespread infiltrates in comparison to the often-localised consolidation of early bacterial pneumonia.

Pharyngitis

Although most throat infections in pregnancy are of viral original and non-severe, approximately 10 % are caused by *Group A Streptococcus*, which can result in genitourinary and systemic infections [54]. If three of the four Centor criteria are present (fever, tonsillar exudate, no cough, tender anterior cervical lymphadenopathy), appropriate antibiotics should be commenced, most commonly a penicillin [12].

Appendicitis

Appendicitis complicates approximately 1 in 1500 pregnancies and can be difficult to diagnose as the appendix is deflected by the expanding fundus, leading to unusual sites of pain and tenderness. The appendix is more likely to rupture during pregnancy (up to 20 %) as the displaced omentum is less able to contain an inflamed appendix [46].

Clinical features include abdominal pain and tenderness, nausea, fever and leucocytosis. Diagnosis is usually made clinically although the risks and benefits of CT imaging must be weighed against the potential for an unnecessary operation if the diagnosis is in doubt [46].

Cholecystitis

Gallstone disease can occur in up to 10 % of pregnancies [68], and acute cholecystitis occurs when there is obstruction of the cystic duct with bacterial infection complicating in up to 85 % of these cases. Clinical features include right upper quadrant pain, fever, nausea and leucocytosis. Diagnosis can be confirmed with non-invasive ultrasound scanning. Conservative management with antibiotics and intravenous fluids may be sufficient, but surgical cholecystectomy may be required in non-resolving cases or in complications such as pancreatitis. Endoscopic retrograde cholangiopancreatography may be beneficial in common bile duct obstruction [46].

Pyelonephritis

The incidence of pyelonephritis in pregnancy is estimated to be 2 % [70]. Early signs and symptoms include dysuria and flank pain and tenderness alongside the more non-specific symptoms of nausea, chills and rigours. Patients may present at any stage of pregnancy, including post partum, although 90 % occur prior to delivery [70]. Specific investigations will include urinalysis with urine microscopy and culture alongside ultrasound scanning of the renal tracts to exclude structural abnormalities or the presence of renal calculi. Screening for and treating asymptomatic bacteriuria in pregnancy reduces the risk of developing pyelonephritis from 20–35 % to 1–4 % [20].

The most common causative organisms include Gram-negative bacilli such as *Escherichia coli* or *Klebsiella* species although other organisms such as *Group B Streptococci* can contribute [70]. The presence of resistant organisms such as extended-spectrum beta lactamase (ESBL) organisms should be considered in women with long-term urinary catheter insertion, prolonged or repeated hospital admissions or long-term residence in a healthcare facility. Such women should be managed with the input of specialist microbiology services and may require carbapenem therapy [54].

Risk factors for the development of pyelonephritis include multiparity, diabetes mellitus, urinary tract stones or malformations and low socioeconomic status [70].

Women with pyelonephritis are more likely to develop anaemia (OR 2.6), septicaemia (OR 56.5), acute kidney injury (OR 16.5), preterm birth (OR 1.3), low birth weight birth (OR 1.3), chorioamnionitis (OR 1.3) and Caesarean delivery (OR 1.2) compared to women without [70].

Tuberculosis

Tuberculosis, whilst still relatively uncommon in the developed world, has an increasing incidence and already represents a huge burden of disease within the developing world [39].

Screening (tuberculin skin test or interferon-gamma release assay test) should be considered in the following situations:

- Close contact with a patient with active TB.
- Concomitant HIV infection.
- Immunocompromised patients.
- Symptoms of TB (weight loss, night sweats, fever and cough).
- Illegal drug users.
- Patients from endemic areas should be managed with a high degree of suspicion (Latin America, Caribbean Africa, Asia, Eastern Europe, Russia) [46].

It should be noted that TB might present differently in pregnancy, with up to half presenting

with non-specific symptoms and extra pulmonary disease [39].

Severe sepsis is uncommon in TB but may occur in those who are immunocompromised such as patients with HIV, and treatment for latent TB is recommended in these patients as the rate of conversion to active TB is approximately 8 % [11]. Involvement of the infectious disease team is vital in these situations and in particular when extra pulmonary disease is suspected.

HIV

HIV is the leading cause of death amongst women of childbearing age in sub-Saharan Africa, and this region also displays the highest rates of maternal mortality [72]. The rate of maternal mortality amongst women with HIV is eight times higher than non-infected women, and this may be as the result of pregnancy accelerating the progression of HIV or HIV increasing the risk of obstetric complications generally [9].

Whilst maternal mortality in women with HIV is difficult to quantify due to a paucity of data, one review identified that 12 % of pregnancy-related deaths occurred as the result of HIV in a region with an overall HIV incidence of 2 %. When the HIV incidence rose to 15 %, the mortality attributable to HIV was 50 %. The authors concluded, based on the estimated incidence of HIV worldwide, that 5 % of pregnancy-related deaths worldwide and 25 % in sub-Saharan Africa are attributable to HIV infection [10].

Looking specifically at sepsis in HIV-infected pregnant women, those who had a vaginal delivery had a rate of infection three times higher than the non-HIV pregnant women, with the increased risk elevated to six times should a Caesarean delivery be undertaken. Women with HIV had an increased risk of wound infection (OR 1.75) and endometritis (OR 1.86) [9].

Benefits have been seen when HIV-infected women are given prophylactic antibiotics during labour [58]; however, the most important modifiable factor in reducing both sepsis and all-cause mortality is ensuring access to antiretroviral therapy for affected individuals [73]. Consultation with an infectious disease specialist is advised with local protocols on the management of pregnant women with HIV infection developed in order to improve outcomes, particularly in regions with high rates of infection.

Malaria

Pregnant women infected with the malarial parasite *Plasmodium falciparum* are at an increased risk of maternal anaemia, low birth weight, intrauterine growth restriction and preterm birth, and many of the effects are thought to occur as the result of placental sequestration. Pregnant women have a three times increased risk of contracting severe malaria compared to the non-pregnant population [56].

Diagnosis of malaria in pregnancy can be challenging as parasites may sequester in the placenta but be undetectable in peripheral blood smears. Placental sampling may be required to confirm diagnosis [25].

The mortality of infection with P. falciparum can approach 50 % in pregnancy. Clinical features are often non-specific and include fatigue, headache and fever with progression to seizures, pulmonary oedema, renal failure and jaundice if untreated [69]. History of travel to an endemic area should be actively sought.

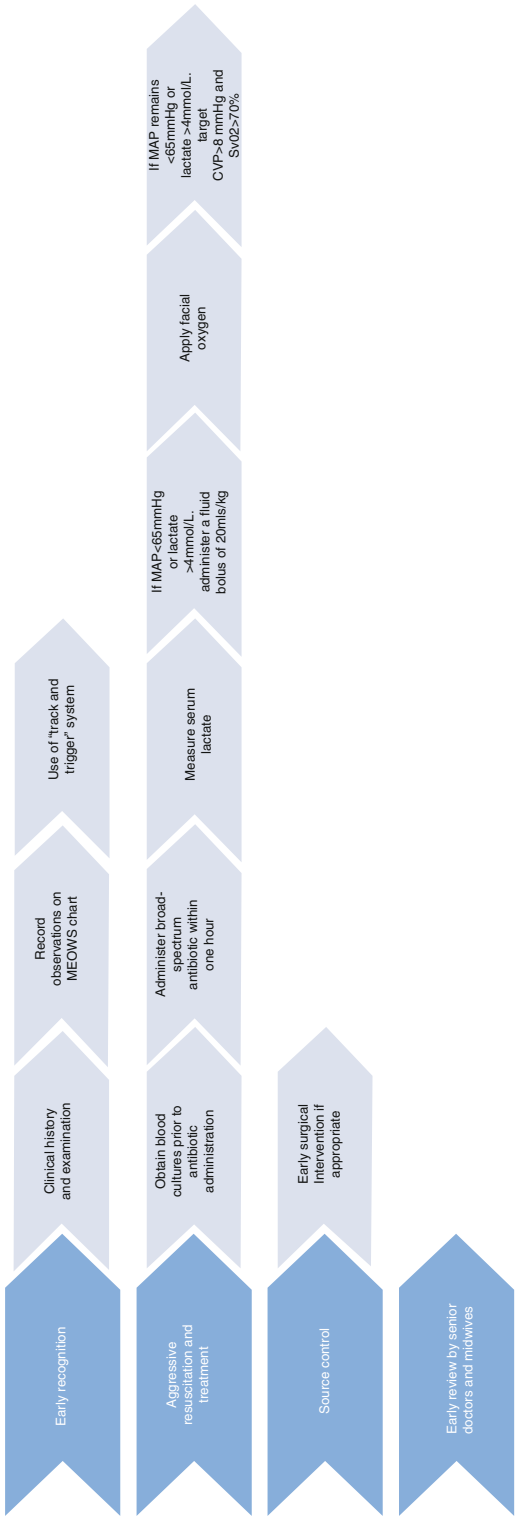
For severe, falciparum malaria, intravenous artesunate is the treatment of choice, with quinine used if artesunate is unavailable. Quinine and clindamycin should be used in uncomplicated falciparum or mixed malaria and chloroquine for other malarial parasites. Primaquine is contraindicated in pregnancy and advice from local infectious disease specialists sought early [55].

Complications of malaria that should be identified early and treated if possible include hypoglycaemia, pulmonary oedema, anaemia, hyperpyrexia, seizures, metabolic acidosis, coagulopathy, renal failure and secondary bacterial infections [55].

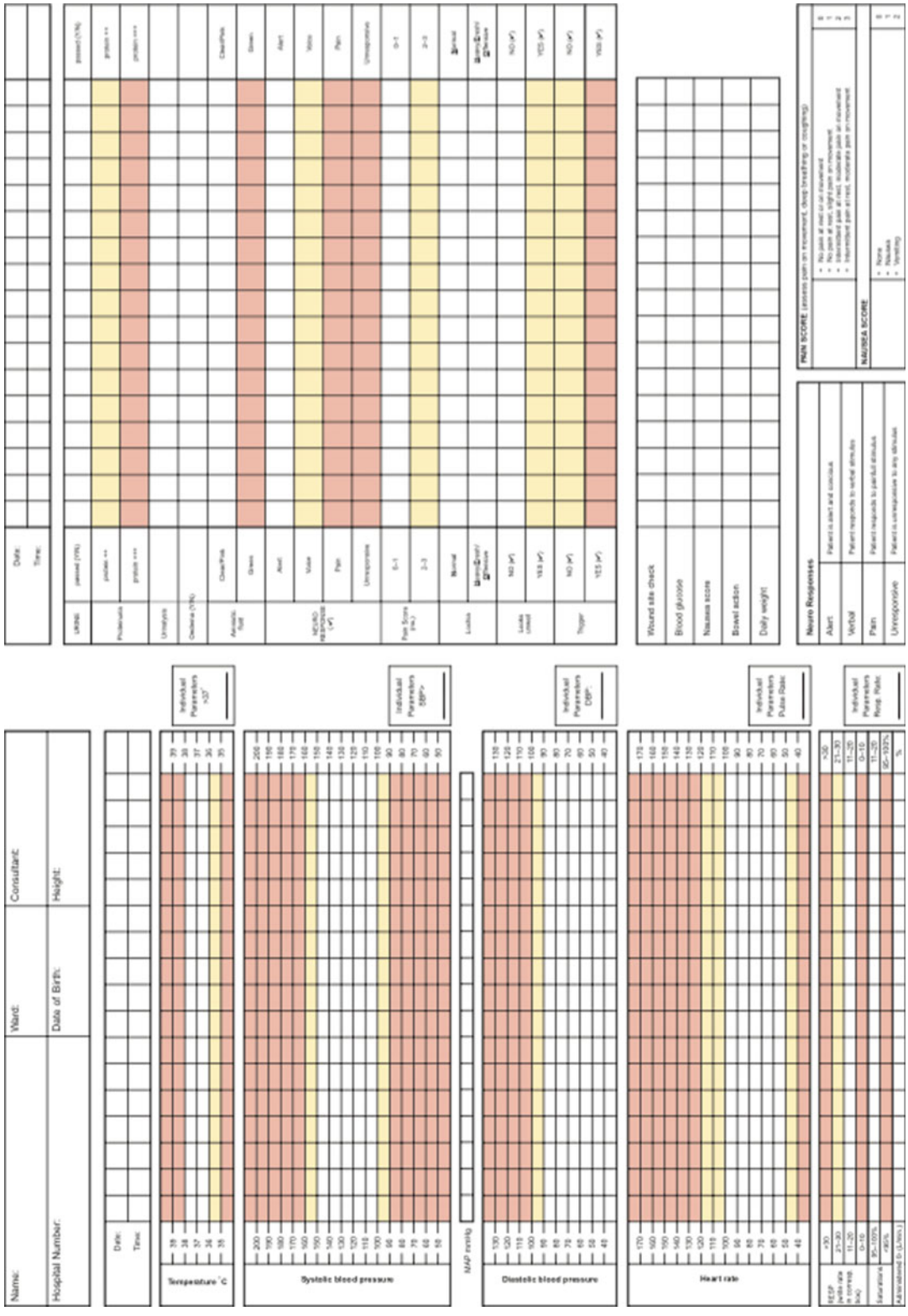
Conclusion

Maternal sepsis remains a significant contributor to maternal mortality, but its impact can be lessened with early recognition, aggressive resuscitation and treatment, source control and input from senior medical, nursing and midwifery staff.

Appendix 1: Algorithm for Management of Maternal Sepsis



Appendix 2: Sample MEOWS Chart [59]



References

1. Acosta CD, Bhattacharya S, Tuffnell D, et al. Maternal sepsis: a Scottish population-based case-control study. Br J Obstet Gynaecol. 2012;119:474–83.
2. Acosta C, Knight M, Lee H, et al. The continuum of maternal sepsis severity: incidence and risk factors in a population-based cohort study. PLoS One. 2013;8(7):e67175.
3. Acosta C, Kurinczuk J, Lucas D, et al. Severe maternal sepsis in the UK, 2011–2012: a national case-control study. PLoS Med. 2014;11(7):e1001672.
4. Annane D, Sébille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA. 2002;288:862–71.
5. Arulkumaran N, Singer M. Puerperal sepsis. Best Pract Res Clin Obstet Gynaecol. 2013;27:893–902.
6. Barton J, Sibai B. Severe sepsis and septic shock in pregnancy. Obstet Gynecol. 2012;120:689–706.
7. Brunkhorst FM, Engel C, Bloos F, German Competence Network Sepsis (SepNet), et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358:125–39.
8. Caironi P, Tognoni G, Masson S, for the ALBIOS Study Investigators, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med. 2014;370:1412–21.
9. Calvert C, Ronsmans C. HIV and the risk of direct obstetric complications: a systematic review and meta-analysis. PLoS One. 2013;8(10):e74848. doi:10.1371/journal.pone.0074848.
10. Calvert C, Ronsmans C. The contribution of HIV to pregnancy-related mortality: a systematic review and meta-analysis. AIDS. 2013;27:1631–9.
11. Centers for Disease Control and Prevention. Treatment of tuberculosis. MMWR Recomm Rep. 2003; 52(RR–11):1–77.
12. Centor RM, Witherspoon JM, Dalton HP, et al. The diagnosis of strep throat in adults in the emergency room. Med Decis Making. 1981;1:239–46.
13. Centre for Maternal and Child Enquiries (CMACE). Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006–08. The eighth report on confidential enquiries into maternal deaths in the United Kingdom. BJOG. 2011;118 Suppl 1:1–203.
14. Centre for the Enquiry into Maternal and Child Health (CEMACH). Saving mothers' lives: reviewing maternal deaths to make motherhood safer 2003–2005. In: Lewis G, editor. The seventh confidential enquiry into maternal deaths in the United Kingdom. London: CEMACH; 2007.
15. Cullinane M, Findlay G, Hargraves C, Lucas S. An acute problem? London: National Confidential Enquiry into Patient Outcome and Death; 2005.
16. Delaney AP, Dan A, McCaffrey J, et al. The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta- analysis. Crit Care Med. 2011;39:386–91.
17. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock. Intensive Care Med. 2013;39(2):165–228.
18. Department of Health and the Royal College of Obstetricians and Gynaecologists. Pandemic H1N1 2009 influenza: clinical management guidelines for pregnancy. London: RCOG press; 2009.
19. Department of Health. Clinical guidelines for immunoglobulin use. 2nd ed. 2008. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_085235.
20. Duff P. Pyelonephritis in pregnancy. Clin Obstet Gynecol. 1984;27:17–31.
21. Edwards R. Chorioamnionitis and labor. Obstet Gynecol Clin North Am. 2005;32:287–96.
22. Faro C, Faro S. Postoperative pelvic infections. Infect Dis Clin North Am. 2008;22:653–63.
23. Finfer S, Bellomo R, Boyce N, SAFE Study Investigators, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350:2247–56.
24. Fjerstad M, Trussell J, Sivin I, et al. Rates of serious infection after changes in regimens for medical abortion. N Engl J Med. 2009;361:145–51.
25. Fried M, Muehlenbachs A, Duffy P. Diagnosing malaria in pregnancy: an update. Expert Rev Anti Infect Ther. 2012;10(10):1177–87.
26. Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ. 2009;180:821–7.
27. Guidet B, Martinet O, Boulain T, et al. Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: the CRYSTMAS study. Crit Care. 2012;16:R94.
28. Heslehurst N, Ells LJ, Simpson H, Batterham A, Wilkinson J, Summer- bell CD. Trends in maternal obesity incidence rates, demographic predictors, and health inequalities in 36,821 women over a 15-year period. Br J Obstet Gynaecol. 2007;114:187–94.
29. Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med. 2014;371:1381–91.
30. Hussein J, Walker L. Puerperal sepsis in low- and middle-income settings: past, present and future. In: Kehoe S, Neilson J, Norman J, editors. Maternal and infant deaths: chasing millennium development goals 4 and 5. London: RCOG; 2010.
31. Jansen TC, van Bommel J, Schoonderbeek FJ, et al. Early lactate-guided therapy in intensive care unit patients: a multi-center, open-label, randomized controlled trial. Am J Respir Crit Care Med. 2010;182(6):752–61.
32. Jin Y, Carriere KC, Marrie TJ, et al. The effects of community-acquired pneumonia during pregnancy ending with a live birth. Am J Obstet Gynecol. 2003;188:800–6.

33. JPAC – Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee. Guidelines for the blood transfusion services in the UK. 8th ed. London: TSO; 2013. http://www.transfusionguidelines.org.uk. Accessed 11 Dec 2014.
34. Kakkos SK, Caprini JA, Geroulakos G, et al. Combined intermit- tent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism in high-risk patients. Cochrane Database Syst Rev. 2008;4:CD005258.
35. Kansagara D, Fu R, Freeman M, et al. Intensive insulin therapy in hospitalized patients: a systematic review. Ann Intern Med. 2011;154:268–82.
36. Kaye DK, Kakaire O, Osinde MO. Systematic review of the magnitude and case fatality ratio for severe maternal morbidity in sub-Saharan Africa between 1995 and 2010. BMC Pregnancy Childbirth. 2011;11:65.
37. Khan KS, Wojdyla D, Say L, et al. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367(9516):1066–74.
38. Knight M, Kenyon S, Brocklehurst P, on behalf of MBRRACE-UK, et al., editors. Saving lives, improving mothers' care – lessons learned to inform future maternity care from the UK and Ireland confidential enquiries into maternal deaths and morbidity 2009–12. Oxford: National Perinatal Epidemiology Unit, University of Oxford; 2014.
39. Knight M, Kurinczuk J, Nelson-Piercy C, Spark P, Brocklehurst P, on behalf of UKOSS. Tuberculosis in pregnancy in the UK. Br J Obstet Gynaecol. 2009;116:584–8.
40. Kramer H, Schutte J, Zwart J, et al. Maternal mortality and severe morbidity from sepsis in the Netherlands. Acta Obstet Gynecol Scand. 2009; 88:647–53.
41. Lamont RF, Sobel JD, Carrington D, et al. Varicella-zoster virus (chickenpox) infection in pregnancy. Br J Obstet Gynaecol. 2011;118:1155–62.
42. Lappen J, Keene M, Lore M, et al. Existing predictive models do not accurately characterise risk of sepsis in obstetric patients. Am J Obstet Gynaecol. 2009; (6):S231–2.
43. Leibovici L, Shraga I, Drucker M, et al. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. J Intern Med. 1998; 244:379–86.
44. Levy M, Rhodes A, Phillips G, et al. Surviving sepsis campaign: association between performance metrics and outcomes in a 7.5-year study. Intensive Care Med. 2014;40(11):1623–33.
45. Metersky M, Ma A, Bratzler D, Houck P. Predicting bacteremia in patients with community-acquired pneumonia. Am J Respir Crit Care Med. 2004; 169(3):342–7.
46. Morgan J, Roberts S. Maternal sepsis. Obstet Gynecol Clin N Am. 2013;40:69–87.
47. Muthuri SG, Venkatesan S, Myles PR, Leonardi- Bee J, Al Khuwaitir TS, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med. 2014;2(5):395–404.
48. Myburgh JA, Finfer S, Bellomo R, CHEST Investigators, Australian and New Zealand Intensive Care Society Clinical Trials Group, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367:1901–11.
49. Naleway AL, Irving SA, Henninger ML, Li DK, Shifflett P, et al. Safety of influenza vaccination during pregnancy: a review of subsequent maternal obstetric events and findings from two recent cohort studies. Vaccine. 2014;32(26):3122–7.
50. National Institute of Clinical Excellence. Venous thromboembolism: reducing the risk. NICE Clinical Guideline 92. Issued January 2010.
51. Perner A, Haase N, Guttormsen A, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367(2):124–34.
52. PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Critical Care Medicine Trials Group, Cook D, Meade M, Guyatt G, et al. Dalteparin versus unfractionated heparin in critically ill patients. N Engl J Med. 2011;364:1305–14.
53. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345:1368–77.
54. Royal College of Gynaecologists. Bacterial sepsis in pregnancy. Green-top guideline No. 64a. London: RCOG press; 2012.
55. Royal College of Gynaecologists. The diagnosis and treatment of malaria in pregnancy. Green–top Guideline No. 54b. London: RCOG press; 2010.
56. Sappenfield E, Jamieson D, Kourtis A. Pregnancy and susceptibility to infectious diseases. Infect Dis Obstet Gynecol. 2013;2013, 752852. doi:10.1155/2013/752852. 8 pages.
57. Say L, Chou D, Gemmill A, Tunçalp O, Moller A, Daniels J, Gülmezoglu A, Temmerman M, Alkema L. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2:e323–33.
58. Sebitloane HM, Moodley J, Esterhuizen TM. Prophylactic antibiotics for the prevention of postpartum infectious morbidity in women infected with human immunodeficiency virus: a randomized controlled trial. Am J Obstet Gynecol. 2008;198:189.e181–6.
59. Singh S, McGlennan A, England A, Simons R. A validation study of the CEMACH recommended modified early obstetric warning system (MEOWS). Anaesthesia. 2012;67:12–8.
60. Soliman HM, Vincent JL. Prognostic value of admission serum lactate concentrations in intensive care unit patients. Acta Clin Belg. 2010;65(3):176–81.
61. Sprung CL, Annane D, Annane D, Keh D, CORTICUS Study Group, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008; 358:111–24.

62. Sriskandan S. Severe peripartum sepsis. J R Coll Physicians Edinb. 2011;41:339–46.
63. Steer JA, Lamagni T, Healy B, Morgan M, Dryden M, et al. Guidelines for prevention and control of group A streptococcal infection in acute healthcare and maternity settings in the UK. J Infect. 2012;64(1):1–18.
64. The ARISE Investigators and the ANZICS Clinical Trials Group. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371:1496–506.
65. The NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–97.
66. Timezguid N, Das V, Hamdi A, et al. Maternal sepsis during pregnancy or the postpartum period requiring intensive care admission. Int J Obstet Anaesth. 2012;21(1):51–5.
67. United Nations. United Nations Millennium Development Goals. 2013. http://www.un.org/millenniumgoals/maternal.shtml. Accessed 12 Nov 2014.
68. Valdivieso V, Covarrubias C, Siegel F, et al. Pregnancy and cholelithiasis: pathogenesis and natural course of gallstones diagnosed in early puerperium. Hepatology. 1993;17:1.
69. White N, Pukrittayakamee S, Hien T, et al. Malaria. Lancet. 2014;383:723–35.
70. Wing DA, Fassett MJ, Getahun D. Acute pyelonephritis in pregnancy: an 18-year retrospective analysis. Am J Obstet Gynecol. 2014;210:219.e1–6.
71. World Health Organisation. World Health Statistics 2014: part 1 health-related millennium development goals. Geneva; 2014. http://www.who.int/gho/publications/world_health_statistics/EN_WHS2014_Part1.pdf?ua=1. Accessed 12 Nov 2014.
72. World Health Organization. Trends in maternal mortality: 1990 to 2008. Geneva: World Health Organization; 2010.
73. World Health Organization. Antiretroviral drugs for treating pregnant women and preventing HIV infections in infants: recommendations for a public health approach, 2010 version. Geneva; 2010.
74. Yealy DM, Kellum JA, Juang DT, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370:1683–93.
75. Yudkin M. Risk management of seasonal influenza during pregnancy: current perspectives. Int J Women's Health. 2014;6:681–9.